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(54) Title: ORALLY DISINTEGRATING TABLETS

(57) Abstract: Silicified microcrystalline cellulose is used to provide a tablet with oral disintegration. The tablet contains at least 30% of the silicified microcrystalline cellulose and an effective amount of a pharmaceutically active agent.

ORALLY DISINTEGRATING TABLETS

Background of the Invention

The present invention relates to orally disintegrating dosage forms that contain silicified microcrystalline cellulose.

Orally disintegrating dosage forms for delivery of pharmaceuticals are known in the art. The purpose of such systems is to allow administration of a solid dosage form, for instance a tablet, of a beneficial drug to a patient without the need to swallow the dosage form. The orally disintegrating tablet should disintegrate and, optionally dissolve, directly in oral cavity, with the aid of saliva or, in some cases a small amount of water. The resulting liquid or dispersion is then easily swallowed. This causes easy and immediate entry of the dissolved or dispersed beneficial drug into the gastrointestinal tract. In some cases the drug may even be absorbed by the oral mucosa or the esophageal lining as it passes down to the stomach. Orally disintegrating tablets, contrary to candies or sublingual tablets, should disintegrate in a time not exceeding one minute or so in the oral cavity.

The orally disintegrating or dissolving delivery systems are known in the art. One such commercially marketed delivery systems is based on proprietary Zydis® technology (Scherer). This system is based on tablet-shaped freeze-dried solid gelatine or starch matrix network also comprising a water-soluble sugar, such as mannitol. Despite the tablet appearance, such form is actually not made by tabletting, but is a

wafer made by freeze drying of a solution of ingredients in a tablet-shaped "pocket." Such technology is complicated and expensive, requiring special equipment. Similar technologies based on freeze-drying are Lyoc technology (L. Lafon) or QuickSolv technology (Janssen).

Orally disintegrating tablets produced by tabletting are also known. In general, the fast disintegrating/dissolving attribute is achieved by facilitating quick egress of water into the tablet matrix. The basic approaches for making such tablet include maximizing the porous structure of the tablet matrix, incorporating appropriate disintegrating agents, and using highly water-soluble excipients such as sugars or alcohols. Many of the commercial orally dissolving tablets use specifically pre-treated excipients.

One system is Flash Dose technology (Fuisz) in which tablets are made by compressing microparticles of a drug and a cotton candy-like fibrous saccharide matrix (a "floss"). This system requires specific equipment for making the matrix, is sensitive to moisture, and generally results in tablets of high friability.

OraSolv technology (Cima) involves effervescent, microencapsulated tablets. This technique requires specific package technology due to softness and friability of the tablet.

An example of a fast-dissolving conventional tablet is based on Wowtab technology (Yamanouchi), which is a conventionally processed and packed tablet based on a combination of low and high moldability saccharides as tablet excipients (U.S. Patent No. 5,576,014).

Another example is FlashTab technology (Prographarm), which comprises coated microparticles of the active substance (to suppress the unpleasant taste) with excipients. See USP 5,464,632 and 6,106,861. In 6,106,861, for example, a disintegrant and a specific class of water soluble diluent are used to effect oral disintegration properties.

The above techniques tend to require special manufacturing and/or produce tablets that are problematic in terms of water sensitivity, hardness or friability. It would be desirable to have an oral disintegrating tablet that can be made with low friability and by ordinary tabletting techniques.

Separate from oral disintegration concerns, microcrystalline cellulose has been used as a binder especially in direct compression tablet formulations. A modified form of microcrystalline cellulose is taught in US 5,585,115 wherein the microcrystalline cellulose is coprocessed with silicon dioxide to form an intimate mixture. Such a modified cellulose is referred to as silicified microcrystalline cellulose. According to US 5,585,115 silicified microcrystalline cellulose has enhanced compressibility properties, especially in wet granulation conditions, thereby making it more attractive as a binder or diluent in a greater variety of tablet forming processes. Silicified microcrystalline cellulose is commercially available from Penwest under the trade name PROSOLV.

Silicified microcrystalline cellulose has been used to improve certain formulations. For example, WO 99/15155 teaches a pharmaceutical preparation comprising clodronate as the active and silicified microcrystalline cellulose as the excipient. Such compositions can provide good tablet strength, friability,

compressibility, and higher loading of the clodronate. No mention is made in WO 99/15155 of disintegration times or achieving oral disintegration.

Similarly, US 6,190,696 teaches a thyroxine formulation containing a stabilizer. Microcrystalline cellulose, especially silicified microcrystalline cellulose, is taught to enhance the stability of the formulation. More recently published US patent application 20030050312 teaches forming tablets and capsules having low amounts of active, such as less than 3%, by using a mixture of microcrystalline cellulose and silicon dioxide, preferably silicified microcrystalline cellulose. The excipient is reported to increase the homogeneity of the blend. Again, neither of these patent disclosures mentions oral disintegration.

It would be desirable to provide an alternative orally disintegrating tablet having adequate disintegratability and solubility in the oral cavity and sufficient mechanical strength, e.g., to resist destruction in the course of manufacture, storage, transport, and/or use.

Summary of the Invention

The present invention is based on the surprising discovery that orally disintegrating tablets may be made from water insoluble tablet matrix-forming excipients. Accordingly, a first aspect of the invention relates to an orally disintegratable pharmaceutical tablet which comprises an effective amount of a pharmaceutically active agent and a sufficient amount of silicified microcrystalline cellulose such as at least 30%, preferably at least 50%. The tablet disintegrates in less than 90 seconds, preferably 60 seconds or less, more preferably 30 seconds or less. The

tablet optionally contains a disintegrant such as low substituted hydroxypropyl cellulose. The tablets can have conventional hardness, such as 20N to 50N, and low friability, such as 1% or less, while being easily manufactured by conventional techniques. A preferred embodiment relates to an orally disintegrating tablet which disintegrates in 30 seconds or less and which comprises an active agent, the improvement of which comprises providing a matrix of silicified microcrystalline cellulose in an amount of at least 30%, preferably at least 50% , within the tablet.

Another preferred embodiment relates to a pharmaceutical orally disintegratable tablet which consists essentially of 50% to 90% silicified microcrystalline cellulose, 0% to 20% of low substituted hydroxypropyl cellulose, a lubricant, and an effective amount of a pharmaceutically active agent, wherein the tablet exhibits disintegration within 1 to 15 seconds when tested in an *in vitro* disintegration test.

Another aspect of the invention relates to the use of silicified microcrystalline cellulose in making an orally disintegrating tablet.

A further aspect of the invention relates to a process of rapidly releasing an active agent from a solid tablet, which comprises disintegrating a tablet, which comprises at least 30% , preferably at least 50% of a matrix of silicified microcrystalline cellulose and an effective amount of an active agent, by placing the tablet in a water environment for up to 30 seconds.

Description of the Invention

The present invention relates to the surprising discovery that silicified microcrystalline cellulose can be used to provide an orally disintegrable tablet. This ability was not known from the above-recited prior patent disclosures. Indeed, because

silicified microcrystalline cellulose is a water insoluble tablet matrix-forming excipient, the use thereof in providing oral disintegration is contrary to the conventional approach in the art for oral disintegration tablets. The orally disintegrable tablets of the present invention include silicified microcrystalline cellulose as a matrix-forming excipient, typically in amount of at least 30%, typically 50% to 90%, more typically 60% to 80%.

Various embodiments of the orally disintegrating tablets of the present invention may provide one or more of the following features:

- compressible by a known tablet press and packable in a known package;
- portable without fragility concerns, having low friability;
- low sensitivity to environmental conditions such as moisture and temperature;
- able to load a high amount of the drug, resulting in smaller tablet size; and
- leave no or minimal residue in the mouth, have pleasant mouth feel, and be compatible with taste masking.

"Orally disintegratable" means that the tablet disintegrates or disperses within 90 seconds as measured by the *in vitro* disintegration test described in US Pharmacopoeia 701, without disks. Such a disintegration test result is reasonably related to the actual disintegration time experienced by a mammal when placed in the oral cavity (albeit placement within such a cavity is not required). The disintegration of the tablet means that the tablet shape/form is destroyed but does not necessarily mean that the entire tablet is dissolved. For example, insoluble fragments can remain. In general no residue remains on the screen, which has 2 mm mesh size, or only a soft mass having no palpably firm core remains. If coated particles of the active agent are contained within the tablet, as described hereinafter, such particles can be present on the

screen and need not further disintegrate, although typically such particles are too small to be held by the screen mesh and thus are also not present as a residue on the screen. Preferably, the tablets of the present invention disintegrate in less than 80 seconds, more preferably less than 60 seconds including less than 50 seconds and even less than 40 seconds, and most preferably in less than 30 seconds. In some embodiments, the disintegration is not instantaneous, but rather takes at least 0.5 seconds, more preferably at least 2 seconds. In some preferred embodiments, the disintegration occurs within the range of 1 to 30 seconds, more preferably 1 to 20 seconds, still more preferably 1 to 15 seconds, and frequently within 1 to 10 seconds. It should be noted that the corresponding European Pharmacopoeia method generally provides similar results to the above-quoted USP method.

The silicified microcrystalline cellulose (referred sometimes hereinunder as "silicified cellulose") is an intimate physical mixture of colloidal silicon dioxide with microcrystalline cellulose as described in U.S. Patent No. 5,585,115. It is not merely an admixture, but rather an intimate mixture usually formed by mixing the silicon dioxide with a suspension or slurry of microcrystalline cellulose and drying the mixture, such as by spray drying. The amount of silicon dioxide is normally within the range of 0.1 to 20 wt%, preferably from about 0.5 to 10 wt%, more typically from 1.25 to 5 wt%, and conveniently about 2 wt%, based on the weight of the silicified cellulose. The silicon dioxide generally has an average particle size not greater than 100 microns and typically between 5 and 50 microns. The microcrystalline cellulose is not particularly limited and generally has an average particle in the range of 20 to 200 microns. Smaller particles have a practical advantage in that the patient has no or almost no feel of a solid

residue in the mouth upon administration. Larger particles are preferred for optimal powder flow during compression of the tablets. Thus, in most cases, an optimum can be determined based on the subjective preferences of various competing properties through ordinary design and testing experiments. For example, ProSolv 50 and ProSolv 90 (Penwest) are commercially available silicified (2% SiO_2) microcrystalline celluloses having a median particle size of 50 and 90 microns, respectively, and are conveniently used in the present invention. Surprisingly, ProSolv 50 generally has an inferior taste/feeling in the mouth in comparison to ProSolv 90. Thus, silicified microcrystalline cellulose having a median particle size in the range of 75 to 125, especially about 90 microns, are likely preferred from this perspective.

In the tablet of the invention, the disintegration property of silicified cellulose may be enhanced by the presence of a traditional gastric disintegrant. Although such an auxiliary excipient is not necessary, the presence of a disintegrant allows for more homogeneous splitting and breaking of the tablets, a broader range of tablet compaction conditions, and higher loading of the active substance that otherwise may negatively affect the disintegration rate. Generally the amount of disintegrant is within the range of 0 to 20%. When the disintegrant is present, it is typically contained in an amount of 0.1% to 20%, more typically from 0.5% to 15%, still more typically 0.5% to 10% of the tablet mass.

An example of the disintegrant is an hydroxypropyl cellulose (HPC), especially low substituted hydroxypropyl cellulose (L-HPC) as defined in USP. Other suitable disintegrants include sodium starch glycollate, carboxymethyl cellulose, crosscarmelose sodium , crosspovidone, and starch. The disintegrant may be water soluble or insoluble,

but is typically water swellable, which accounts for its disintegrating ability. The disintegrant may be non-hygroscopic. Preferably the disintegrant is not water soluble.

Another excipient that can affect the oral disintegration is a lubricant. A preferred lubricant that tends to facilitate faster disintegration rates is sodium stearyl fumarate, although other lubricants such as magnesium stearate can be used as well. In general, the lubricant should be hydrophilic.

Another factor affecting the disintegration is the tablet hardness and/or the compaction force used in making the tablet hardness. The hardness of the tablet has an influence on the disintegration time as it affects the porosity of the matrix and, accordingly, the ability of water to penetrate through the matrix. The hardness may range from 10 to 50 N, such as about 30 N. If porosity is sufficiently high, water can easily penetrate the tablet.

The size and shape of the tablet can also affect the disintegration time. In general a smaller tablet, in terms of mass, has a faster disintegration time than a larger tablet, all other factors being equal. Similarly, a tablet shape with more surface area generally has a faster disintegration time than a tablet shape having less surface area, all other factors being equal. For pharmaceutical tablets, the weight is generally about 400 mg or less, typically about 100 mg or less, and in some embodiments about 80 mg or less, including 50 mg. In pharmaceutical tablets it is preferred that the pharmaceutically active agent and the silicified cellulose account for at least 80%, preferably at least 85%, more preferably at least 90% of the tablet mass. The shape of a tablet includes round, oval, and polygonal, e.g. pentagonal, octagonal, etc., which can be flat or biconvex. Additionally, the tablet may be scored and/or inscribed. Round tablets and

oval tablets generally have a diameter or length, respectively, of 20 mm or less, such as 5 to 20 mm, more typically 5 to10 mm, such as 8 mm, 6 mm, or 5 mm, but is not limited thereto.

Due to the presence of silicified cellulose, the friability of the tablet is generally less than 1.0%, such as less than 0.5%, or less than 0.2%, as measured according to Pharmacopeia Europea 2.9.7.

Additional auxiliary excipients, which may have no or almost no influence on the disintegration properties, may be present in the tablet composition. Examples of auxiliary excipients include taste masking agents, stabilizers, natural or artificial sweeteners (e.g., aspartame), flavors (e.g., mint flavor), preservatives, and pH adjustors. Other auxiliary excipients may be used in case of need. Water-soluble fillers and binders, commonly used in other orally disintegrating tablets, such as sugars, sugar alcohols, or polyols (e.g., mannitol), are not required to be present and are preferably excluded. They may be present in small amounts, e.g. generally less than 5%, preferably less than 1%, and most preferably 0%. Indeed, in a preferred embodiment, water soluble excipients of any kind, are limited to be not more than 10%, more preferably not more than 5%, more typically not more than 3%, and in some embodiments are 0%, of the total mass of the tablet.

Similarly, effervescent excipients like calcium carbonates, are not required to be present in the inventive composition and are preferably excluded therefrom. The term effervescent excipient includes compounds that evolve gas. For instance, effervescent couples evolve gas by means of chemical reactions that take place upon exposure of the effervescent couple to water and/or to saliva in the mouth. The bubble or gas

generating reaction is most often the result of the reaction of a soluble acid source and alkali metal carbonate or carbonate source. The reaction of these two general classes of compounds produces carbon dioxide gas upon contact with water included in saliva.

The silicified cellulose can exhibit a gritty feeling, albeit not unpleasant, in the mouth after disintegration. By itself, it has no taste and conventional sweeteners or flavors may be used to mask unpleasant tastes that could be caused by the active agent. If such a taste is not masked, the active substance may be pre-treated before adding it into the tablet matrix by measures known in the art, such as by micro- or nano-encapsulation within a coat.

There is no limitation on the active agent useful in the rapid dispersible tablets of the invention. The active substance may be a water-soluble or water-insoluble substance. It may be used in solid, particulate, granular, crystalline, amorphous, or oily form. Generally the active agent is a pharmaceutically active agent, a nutrient, a nutriceutical, or a cosmetic. A nutrient includes food and food additives. A nutriceutical includes vitamins, enzymes, proteins,,etc. that provide a beneficial effect. Whenever appropriate, particles of the active agent, optionally granulated with other excipients, may be coated. For example, a suitable coating (or similarly treatment) for masking an unpleasant taste, improving stability of the active agent and/or for preventing too early absorption of the drug, e.g., by oral mucosa, and/or for controlling the release or absorption of the drug in body fluids can be applied using compositions and techniques known in the art. In particular enteric coatings and extended release coatings can be used to provide an orally disintegratable tablet that provides sustained and/or controlled release of the active agent. The coating could be carried out ,e.g., in a

fluid bed system. The coating material could consists e.g. of polymers (i.e. Eudragit), or waxes (i.e. Precirol, Compritol). Poorly flowable active substances, for instance simvastatin, may be pre-treated by making a granulate with a small amount of a binder and/or with an anti-sticking agent . Such a granulation may be performed by a wet or a dry process. The coated particles (or pretreated drug substance) are then implemented in the standard tablet formulation as will be discussed below.

There is no limitation on the therapeutic class of the active ingredient. Examples of the therapeutic classes of pharmaceutical active agent include:

- antipyretic/analgesic/anti-inflammatory agent,
- antipsychotic/antidepressant agent,
- hypnotic/sedative agent,
- gastrointestinal function conditioning agent,
- antitussive agent,
- antihypertensive/cardiovascular system conditioning agent,
- antiasthmatic/antiallergic agent,
- antiparkinskonic/anti-Alzheimer agent,
- hypolipidemic agents,
- Antimicrobial or antiviral agents
- Chemotherapy agents

The tablets of the invention may also comprise two or more active components, from the same or different therapeutic category and/or active agent category.

There are a number of drug candidates that are ideal for delivery via orally disintegrating dosage forms. Examples include:

- fast-acting medications (e.g., drugs for treating pain, inflammation, migraine, angina, asthma, ulcers, diarrhea, or anxiety)
- compliance-critical medications (e.g., drugs for cardiovascular diseases, hypertension, Parkinson's disease, psychosis, and seizures)
- pediatric medications (e.g., cough/cold/allergy products, analgesics, antipyretics, and antibiotics)

Illustrative and non-limiting examples of pharmaceutical active ingredients formulateable into tablets of the invention, alone in a combination, include: ibuprofen, acetominophen, piroxicam (anti-inflammatory), leflunomide (antirheumatics), ondansetron, granisetron (antiemetics), paracetamol (analgetic), carbamazepin, lamotrigine (antiepileptic), clozapine, olanzapine, risperidone, citalopram, paroxetine, sertraline, fluoxetine, fluvoxamine (antipsychotics/antidepressants), zopiclon, zolpidem (hypnotics), cimetidine, ranitidine, omeprazole (antiulceric), metoclopramide, cisapride, domperidon (prokinetic), zafirlukast, montelukast (antiasthmatics), pramipexol, selegiline (anti-parkinsonics), zolpidem, zopiclon (hypnotics), doxazosin, terazosin, atenolol, bisoprolol, amlodipine, nifedipine, diltiazem, enalapril, captopril, ramipril, losartan (cardiovasculars), glyceroltrinitrate (vasodilantant), alfuzosin, finasteride (urologic), pravastatin, atorvastatin, simvastatin, gemfibrozil (hypolipidemics), metformin (antidiabetic), terfenadine, loratadine (antihistaminic), celecoxib, rifecoxib, rivastigmine.

Olanzapine, Paroxetine, Zolpidem, Montelukast, Pioglitazon, Donepezil, Amlodipine, Anastrozole, Pioglitazon are examples of active substances, at which the pre-treatment by coating may be applied for masking their unpleasant taste.

Wherever appropriate or possible, the active agent can be used as a pharmaceutically acceptable salt, ester, hydrate, or solvate of the base compound. Examples of suitable pharmaceutically acceptable salts with acids are hydrochloride, hydrobromide, sulfate, carbonate, nitrate, phosphate, acetate, propionate, butyrate, malonate, maleate, fumarate, citrate, lactate, mandelate, malate, tartrate, adipate, methane sulfonate, benzene sulfonate, p-toluene sulfonate, and 2-hydroxyethane sulfonate, all as hemi- mono- or di-salts. Examples of salts with bases are sodium, potassium, calcium, ammonium, ethanol amine, diethanolamine, ethylenediamine, and N-methylglucamine. Examples of esters are methyl, ethyl, isopropyl, tert. butyl, and benzyl. Examples of hydrates are hemihydrate, monohydrate, sesquihydrate, dihydrate, hemipentahydrate, trihydrate, and tetrahydrate. Examples of solvates are methanolate , ethanolate, and acetonate. The invention is also not limited to a particular polymorph or enantiomer of such active ingredient.

The amount of the active ingredient in a single tablet is generally effective for its intended purpose. Usually an effective amount is within the range of 0.01 to 100 mg, more typically 0.1 to 40 mg, especially 1 to 20 mg. In relative terms, the active agent is generally present from 0.01 to 50% of the tablet mass, preferably 1 to 30%, more typically 5 to 20%.

A preferred class of tablets has the following recipe:

	%/Tablet
Active agent (preferably pharmaceutical active agent)	X
Silicified microcrystalline cellulose	90.5-X
L-HPC	5.0
Sweetener (e.g. aspartame)	2.0
Flavorant (e.g. mint flavor)	2.0
Lubricant (e.g. sodium stearyl fumarate)	0.5
Tablet weight	100.0

The tablets of the present invention can be made from ingredients that are known, commercially available or readily obtainable, via known or analogous synthetic routes, using techniques generally known in the art. Any tabletting method can be used for making the orally disintegrating tablets of the invention. The tablets may be made by dry granulation, wet granulation, or direct compression. Direct compression is technically simple and economically advantageous. As mentioned above, the tabletting technique should produce an appropriate hardness for the composition, weight, shape, etc. of the tablet so as to allow for oral disintegration.

No specific pretreatment step is necessary to modify the properties of the tablet matrix-forming disintegrable components before compression into a tablet. Direct compression may involve direct compression of a homogeneous mixture of the components. The homogenization of the mixture may be made without the aid of a

solvent. Also, the ingredients need not be subjected to enhanced temperature during the homogenization. The active agent might be subjected to a suitable pre-treatment, e.g., a granulation or coating, e.g., to improve compression properties, to modify its release rate, or to mask its taste.

Wet granulation can also be used to make the tablets of the invention wherein the active agent is wet granulated with all or most of the silicified microcrystalline cellulose to form granules. The granules are mixed with the remaining excipients, typically a lubricant and any remaining silicified microcrystalline cellulose, to form a tablet blend and then compressed into tablets. Typically in a wet granulation process, all of the silicified microcrystalline cellulose is within the granulate and no extra-granular silicified microcrystalline cellulose is employed. This is in contrast to the direct compression methods wherein even if a wet granulation pre-treatment is used, most and preferably all of the silicified microcrystalline cellulose is extra-granular; i.e. not used in the pretreatment.

Depending upon the size and shape, the tablet may advantageously be made under a compression force of below 5 kg/cm^2, such as below about 4 kg/cm^2, or below 3 kg/cm^2.

The tablet making process results in a binder matrix of silicified cellulose having the active agent dispersed therein. The process of making the tablet composition does not require the use of compounds or processes for improving the porosity or permeability of the tablet matrix. Thus, pore forming agents, foaming agents, or similar tools may or may not be used in making tablet compositions of the invention.

The tablets of the invention may be easy to administer and may improve patient's compliance. For instance, conventional alendronate tablets must be administered on an empty stomach upon awakening with a full glass of water, and the patient must remain upright for 30 to 60 minutes, as esophagitis may result if the tablet stays in the esophagal region. An orally dispersible tablet may be administered without such caution.

In addition, there are many types of patients that could benefit from orally disintegrating dosage forms, such as pediatric patients, psychiatric patients, patients with renal disorders or patients with swallowing disorders. Dysphagia or difficulty in swallowing is seen to afflict nearly 35% of the general population.

In addition to ease of delivery, another potential advantage of orally disintegrating dosage forms is that they can improve the overall clinical performance of a drug by reducing the incidence of non-compliance.

The rapidly disintegrating tablets of the invention can provide a process for quickly releasing the active agent from a solid tablet. Specifically, in a preferred embodiment, the tablets can be used by placing them in a water environment for up to 30 seconds. In 30 seconds or less the tablet is disintegrated in the water environment, i.e. the tablet is no longer in existence or present in the water environment, albeit a residue thereof may be present. The destruction of the tablet allows the release of the active agent; i.e. as a per se compound, as a particle such as a coated particle, etc., as discussed above for forms of the active agent. The water environment can be any moist environment including an oral cavity, a container of water such as the disintegration apparatus or a glass of water, etc. In case of a glass of water or other similar water

container, a patient may consume the product after, or even during, disintegration. In this way, the once solid dosage form is consumed as essentially a liquid, including a suspension or slurry. It is surprising that a solid tablet containing silicified cellulose could be disintegrated by contacting it with water for 30 seconds or less as the use of silicified cellulose as a rapid disintegrant and/or oral disintegrant is not described in the above-mentioned patent disclosures.

When administering the tablet to an animal, one or more tablets may be used in order to achieve the intended dose of the active agent. Such multiple tablets can be given simultaneously or sequentially, normally within a few minutes of each other.

The disclosure in each of the above-mentioned patents and published patent applications is incorporated herein in its entirety. The present invention will be further illustrated by way of the following Examples. These Examples are non-limiting and do not restrict the scope of the invention.

EXAMPLES

Example 1: Orally disintegrating tablets containing Leflunomide

The composition of this Example is shown in Table 1, below.

TABLE 1

Example 1	mg/tablet	%/tablet
Leflunomide	20.0	20.00
Silicified microcrystalline cellulose	74.5	74.50
L-HPC (low substituted hydroxypropylcellulose)	5.0	5.00
Magnesium stearate	0.5	0.50
Tablet weight	100.0	100.00

Leflunomide, silicified microcrystalline cellulose, and L-HPC were homogeneously mixed with a Turbula mixer. The magnesium stearate was added and mixing was finalized. 6 mm round biconvex tablets were compressed in a tablet press to a hardness of 46 N.

The friability of the tablets was well below 1.0 %.

The disintegration time as measured with the USP disintegration apparatus was less than 10 seconds.

Example 2-3

Both examples were prepared as described in Example 1, except that the composition was modified as discussed below and the tablet punch was changed to an oval, biconvex tablet punch with a length of 6 mm and having an inscription "ABO" therein.

Example 2: Leflunomide orally disintegrating tablet with sodium stearyl fumarate

The composition of this Example is shown in Table 2, below.

TABLE 2

	mg/tablet	%/tablet
Leflunomide	10.00	20.00
Silicified microcrystalline cellulose	37.75	74.50
L-HPC	2.50	5.00
Sodium stearyl fumarate	0.25	0.50
Tablet weight	50.0	100.00

In this case the desintegration time of the tablets was very quick. In 5 seconds the tablets had disappeared in the disintegration test.

Example 3: Leflunomide orally disintegrating tablet with double L-HPC

The composition of this Example is shown in Table 3, below.

TABLE 3

	mg/tablet	%/tablet
Leflunomide	20.0	20.00
Silicified microcrystalline cellulose	69.5	69.50
L-HPC	10.0	10.00
Sodium stearyl fumarate	0.5	0.50

The desintegration time of the tablets was extremely quick. In 1-2 seconds the tablets had disappeared.

Example 4: Orally disintegrating tablet containing ondansetron

The composition of this Example is shown in Table 4, below.

TABLE 4

	mg/tablet	%/tablet
Ondansetron base	8.00	13.9
Silicified microcrystalline cellulose	37.50	65.4
L-HPC	3.50	6.1
Aspartame	7.70	13.4
mint flavor	0.40	0.6
Sodium stearyl fumarate	0.25	0.4
Tablet weight	57.35	100.0

The ondansetron base, silicified microcrystalline cellulose, L-HPC, aspartame, and mint flavor were mixed for 15 minutes in a Turbula mixer. The sodium stearyl fumarate was added, and the mixture was mixed for 5 minutes. The tablets were pressed using a Korsch EK0 tablet press at various compression forces. The disintegration time was directly dependent on the hardness. The tablets having a

hardness within the range of 10-40 N fulfilled the desirable fast disintegration criteria. The friability of the 10-40 N hardness tablets was still close to 0 %. The taste of the active ingredient and the gritty feel of the silicified microcrystalline cellulose was counteracted by the aspartame and mint.

Example 5: Orally disintegrating tablet containing ondansetron free base

The composition of this Example is shown in Table 5, below.

TABLE 5

	mg/tablet	%/tablet
Ondansetron base	8.00	8.00
Silicified microcrystalline cellulose	82.50	82.50
L-HPC	5.00	5.00
Aspartame	2.00	2.00
mint flavour	2.00	2.00
Sodium stearyl fumarate	0.50	0.50
Tablet weight	100.00	100.00

The ondansetron base, silicified microcrystalline cellulose, L-HPC, aspartame and mint flavor were mixed for 15 minutes in a Turbula mixer. The sodium stearyl fumarate was added, and the mixture was mixed for 5 minutes. 8 mm round biconvex tablets were compressed on a Korsch PH 106 tablet press at a target hardness of 30 N. During compression no problems were observed. The tablets dispersed within 30 seconds when placed in the mouth.

Example 6-12: Orally desintegrating tablets containing a range of actives

In the following examples the same concept was applied to various actives, differing in solubility, dose, and/or therapeutic area.

The generic formula for all cases is shown in Table 6, below:

TABLE 6

	%/tablet
Active drug substance	X
Silicified microcrystalline cellulose	90.5 - X
L-HPC	5.00
Aspartame	2.00
mint flavor	2.00
Sodium stearyl fumarate	0.50
Tablet weight	100.00

X= amount of drug substance used.

The manufacturing procedure for all was similar. The active drug substance, silicified microcrystalline cellulose, L-HPC, aspartame and mint flavor were mixed for 15 minutes in a Turbula mixer. The sodium stearyl fumarate was added, and the mixture was mixed for 5 minutes. In all cases, 8 mm round biconvex tablets were pressed using a Korsch EK0. Tablet hardness is 30 N, friability below 1.0 %.

Example 6: Orally disintegrating tablet containing olanzapine

Orally disintegrating tablets containing 20 mg of olanzapine and 70.5 mg of silicified microcrystalline cellulose were prepared following the above general instructions. The disintegration time in the mouth of the product was less than 30 seconds.

Example 7: Orally disintegrating tablet containing montelukast sodium

Orally disintegrating tablets containing 10.4 mg of montelukast sodium were prepared following the instructions as described above. A disintegration test with the Ph. Eur apparatus showed that the tablets disintegrated within 30 seconds.

Example 8: Orally disintegrating tablets containing risperidone free base

Orally disintegrating tablets were prepared by following the general instructions described above. 4 mg of risperidone base was incorporated in the formula. The disintegration of the tablet in the mouth took less than 30 seconds. Also, the bitter taste of risperidone was masked by the mint and aspartame present in the formula.

Example 9: Orally disintegrating tablets containing pramipexol

Orally disintegrating tablets containing 1.5 mg of pramipexol dihydrochloride were prepared by following the general instructions. The tablets disintegrated within 30 seconds when placed in the mouth.

Example 10: Orally disintegrating tablet containing alendronate sodium.

Orally disintegrating tablets containing 13.05 mg of alendronate sodium trihydrate were prepared by following the general instructions presented above. The disintegration time of the tablets as measured by the Ph. Eur. method was less than 1 minute.

Examples 11 and 12: Orally disintegrating tablets containing 10 mg amlodipine (calculated as base)

Orally disintegrating tablets were made containing 10 mg amlodopine base following the general instructions as presented above with two different amlodipine

salts, i.e., 14.28 mg amlodipine besylate monohydrate (Example 11) and 12.8 mg amlodipine maleate (Example 12). In both cases the disintegration time in the mouth was less than 30 seconds.

Example 13 and 14: Orally disintegrating tablets containing 2.5 mg amlodipine (calculated as base)

From the blends as described in Examples 11 and 12, orally disintegrating tablets were prepared containing 2.5 mg of amlodipine (calculated as base). These tablets weighed 25 mg and they disintegrated within 30 seconds after administration.

Example 15: Orally disintegrating tablets containing pre-coated paroxetine mesylate for controlled release purposes

The composition of this Example is shown in Table 7, below.

TABLE 7

	mg/tablet	%/tablet
Paroxetine mesylate	25.83	17.22
Eudragit NE 30 D	10.00	6.66
Silicified microcrystalline cellulose	104.67	69.78
L-HPC	5.00	3.33
aspartame	2.00	1.33
mint flavor	2.00	1.33
Sodium stearyl fumarate	0.50	0.33
Tablet weight	150.00	100.00

Paroxetine mesylate was coated with Eudragit NE 30 D in a fluid bed dryer. The coated particles were mixed with the silicified microcrystalline cellulose, L-HPC, aspartame, and mint flavor in a free-fall mixer. After addition of the sodium stearyl

fumarate the mixing was finalized. Oval biconvex tablets with a length of 8 mm were prepared on an EK0 tablet press. The disintegration time of the tablets as measured by the Ph. Eur. disintegration test was less than 30 seconds. The coated particles remained intact.

Example 16: Orally disintegrating tablets containing Simvastatine

The composition of this Example is shown in Table 8, below.

TABLE 8

	mg/tablet
Simvastatine	10.00
BHA (butylated hydroxyanisol)	0.02
Sodium starch glycolate	0.34
Povidon	0.66
Silicified microcrystalline cellulose	49.46
L-HPC	4.20
aspartame	2.10
mint flavor	2.10
Sodium stearyl fumarate	1.05
Iron oxide yellow	0.07
Tablet weight	70

Pre-treatment:

Simvastatine was granulated with BHA and sodium starch glycolate with Povidon as binder in a high shear granulator. The granulates are subsequently sieved and dried in a fluid bed dryer.

Tabletting

The dried granulate was mixed with the silicified microcrystalline cellulose, L-HPC, aspartame, mint flavor and iron oxide yellow in a free-fall mixer. After addition of the sodium stearyl fumarate the mixing was finalized. Oval biconvex tablets with a

diameter of 7 mm were prepared on an EK0 tablet press. The disintegration time of the tablets as measured by the Ph. Eur. disintegration test was less than 30 seconds.

Example 17. Orally Disintegrating Tablets Comprising Risperidone

	mg/tablet
Risperidon free base	3.0
Silicified microcr. Cellulose Prosolv HD-90	78.90
L-HPC	5.0
Aspartame	6.0
Mint flavour	6.0
Acesulfam K	0.5
Iron oxide red	0.10
Sodium Stearyl Fumarate	0.5

Put the iron oxide through a 100µm sieve.

Mix Risperidone free base, 30% of the Prosolv, L-HPC, Aspartame, Mint flavour, Acesulfame-K and sieved iron oxide by using turbula mixer (22 rpm, 15 min)

Add 70% of the Prosolv and mix for another 15 min at 22 rpm

Sieve Sodium stearyl fumarate through an 800µm sieve.

Add sieved sodium stearyl fumarate and mix for another 5 min at 22 rpm

Compress 100 mg 8 mm tablets at 30 - 40 N on the Korsch EK-0.

The manufactured tablets disintegrate within 30 seconds.

Example 17A: Orally Disintegrating Tablets Comprising Risperidone

Tablets can be made according to the following formulation:

	mg/tablet
Risperidone base	4.0

Silicified Microcrystalline Cellulose	78.0
L-HPC	5.0
Aspartame	6.0
Mint Flavor	6.0
Acesulfam K	0.5
Sodium Stearyl Fumarate	0.5

Tablets are made by mixing the risperidone, aspartame, mint flavor, Acesulfam K, and half of the silicified microcrystalline cellulose in a free fall mixer. Add the second half of the silicified microcrystalline cellulose and mix again. Add the sodium stearyl fumarate and mix again. Compress 8 mm tablets of an average weight of 100 mg and an average hardness between 30 and 40 N.

Example 18 Orally Disintegrating Tablets Containing Paroxetine Mesylate

Granulate	%
POT-mesylate	10
Silicified Microcr. Cellulose Prosolv 90HD	71
PVP	6
Explotab	3
carrageenan 911	10

All ingredients were mixed, granulated and dried in the high shear granulator.

Pretabletting blend	mg/tablet
granulate	90.9
L-HPC	4.55

Mint flavouring spray dried (powder)	1.8
Aspartame Powder	2.3
Sodium Stearyl Fumarate	0.45

Mix the sieved granules with L-HPC, mint and aspartame in a Turbula mixer for 20 minutes at 22 rpm.

Add the sodium stearyl fumarate and mix for 5 minutes at 22 rpm.

Compress tablets using 8 mm punch on EK-0. Target tablet weight=100 mg. Tablet hardness 30N.

Tablets disintegrate within 30 seconds.

Example 19 Orally Disintegrating Tablets Containing Donepezil

Granulate	%
Donepezil-hydrochloride	5
Silicified Microcr. Celulose Prosolv HD-90	78
PVP	6
Explotab	6
Carrageenan 812	5

All ingredients were mixed, granulated and dried in the high shear granulator.

Pretabletting blend	mg/tablet
granulate	90.9
L-HPC	4.55
Mint flavouring spray dried (powder)	1.8
Aspartame Powder	2.3
Sodium Stearyl Fumarate	0.45

Mix the sieved granules with L-HPC, mint and aspartame in a Turbula mixer for 20 minutes at 22 rpm.

Add the sodium stearyl fumarate and mix for 5 minutes at 22 rpm.

Compress tablets using 8 mm punch on EK-0. Target tablet weight=100 mg.

Tablet hardness 30N. Tablets disintegrate within 30 seconds.

Example 20: Orally Disintegrating Tablets Containing Zolpidem (taste masking):

Granulate	mg/tablet
Zolpidem hemitartrate	5.0
Compritol	0.5
Silicified Microcr. Cellulose Prosolv HD-90	44.3
L-HPC	0.25
Aspartame	0.1
Mint flavour	0.1
Sodium Stearyl Fumarate (Pruv)	0.05
Total weight	50

The Zolpidem particles are coated by applying compritol via a Fluid bed process. Afterwards, the coated Zolpidem particles, Prosolv, L-HPC, aspartame and mint flavour are mixed in a free fall mixer, followed by blending the sodium stearyl fumarate. Tablets were prepared on a Korsch EK-0 tablet press at a hardness of 30 N. Tablets disintegrate within 30 seconds.

Example 21: Orally Disintegrating Tablets Containing Tamsulosin Hydrochloride with enteric coating

	mg/tablet
Tamsulosine hydrochloride	0.25
Eudragit	0.038
Triethylcitrate	0.004
Prosolv HD-90	49.225
L-HPC	0.25
Aspartame	0.1
Mint flavour	0.1

Sodium Stearyl Fumarate (Pruv)	0.05
Total weight	50

The tamsulosine particles are coated with Eudragit in a fluid bed system.

The coated granules are mixed with L-HPC, mint and aspartame in a Turbula mixer for 20 minutes at 22 rpm.

Add the sodium stearyl fumarate and mix for 5 minutes at 22 rpm.

Compress tablets using 8 mm punch on EK-0. Target tablet weight=50 mg.

Tablet hardness 30N. Tablets disintegrate within 30 seconds.

In view of the above description of the invention, it will be readily apparent to the worker skilled in the art that the same may be varied in many ways without departing from the spirit of the invention and such modifications are included within the scope of the present invention as set forth in the following claims.

CLAIMS

1. A tablet for oral administration, comprising an effective amount of an active agent and an amount of silicified microcrystalline cellulose, such that said tablet is orally disintegratable.

2. The tablet according to claim 1, wherein said tablet exhibits oral disintegratability in not more than 60 seconds.

3. The tablet according to claims 1 or 2, wherein said tablet exhibits oral disintegratability in not more than 30 seconds.

4. The tablet according to claims 1-3, wherein said tablet exhibits oral disintegratability in not less than 0.5 second.

5. The tablet according to claim 4, wherein said tablet exhibits oral disintegratability in not less than 2 seconds.

6. The tablet according to claim 4, wherein said tablet exhibits oral disintegratability within the range of 1 to 15 seconds.

7. The tablet according to claims 1-6, wherein said silicified microcrystalline cellulose is contained in an amount of at least 30%, preferably within the range of 50% to 90%.

8. The tablet according to claim 7, wherein said silicified microcrystalline cellulose is contained in an amount within the range of 60% to 80%.

9. The tablet according to claims 1-8, wherein said silicified microcrystalline cellulose contains 1-5% silicon dioxide.

10. The tablet according to claims 1-9, wherein said silicified microcrystalline cellulose has an average particle size within the range of 20-200 nm

11. The tablet according to claims 1-10, which further comprises a disintegrant.

12. The tablet according to claim 11, wherein said disintegrant is selected from the group consisting of low substituted hydroxypropyl cellulose, carboxymethyl cellulose, crosscarmelose sodium, crosspovidone, starch, and combinations thereof.

13. The tablet according to claims 12, wherein said disintegrant is low substituted hydroxypropyl cellulose.

14. The tablet according to claims 11-13, wherein said disintegrant is contained in an amount of 0.5% to 20%.

15. The tablet according to claims 1-14, which does not contain an effervescent excipient.

16. The tablet according to claims 1-15, which has a hardness of 20N to 50N.

17. The tablet according to claims 1-16, which has a friability of less than 1%.

18. The tablet according to claims 1-17, wherein said tablet does not contain a water soluble binder.

19. The tablet according to claims 1-18, which further comprises at least one additional excipient selected from the group consisting of taste masking agents, sweeteners, lubricants, stabilizers, preservatives, and pH-adjustors.

20. The tablet according to claims 1-19, wherein said active agent is selected from the group consisting of pharmaceutical active agents, nutrients, nutriceuticals, and cosmetics.

21. The tablet according to claim 20, wherein said active agent is one or more vitamins.

22. The tablet according to claim 20, wherein said active agent is a pharmaceutically active agent.

23. The tablet according to claim 22, wherein said pharmaceutically active agent is present in the form of coated particles containing said pharmaceutically active agent.

24. The tablet according to claim 23, wherein said coating is an extended release or an enteric coating.

25. The tablet according to claims 22-24, wherein said pharmaceutically active agent is selected from the group consisting of anti-inflammatories, antirheumatics, antiemetics, analgetics, antiepileptics, antipsychotics, antidepressants, hypnotics, antiulcerics, prokinetic, antiasthmatics, anti-parkinsonics, cardiovasculars, vasodilators, urologics, hypolipidemics, antidiabetics, and antihistaminics.

26. The tablet according to claims 22-25, wherein said pharmaceutically active agent is selected from the group consisting of ibuprofen, acetominophen, piroxicam, leflunomide, ondansetron, granisetron, paracetamol, carbamazepin, lamotrigine, clozapine, olanzapine, risperidone, citalopram, paroxetine, sertraline, fluoxetine, fluvoxamine, zopiclon, zolpidem, cimetidine, ranitidine,

omeprazole, metoclopramide, cisapride, domperidon, zafirlukast, montelukast, pramipexol, selegiline, zolpidem, zopiclon, doxazosin, terazosin, atenolol, bisoprolol, amlodipine, nifedipine, diltiazem, enalapril, captopril, ramipril, losartan, glyceroltrinitrate, alfuzosin, finasteride, pravastatin, atorvastatin, simvastatin, gemfibrozil, metformin, terfenadine, loratadine, celecoxib, rifecoxib, and rivastigmine, as well as a pharmaceutically acceptable salt, ester; hydrate or solvate of the active agent.

27. A pharmaceutical orally disintegratable tablet which consists essentially of 50% to 90% silicified microcrystalline cellulose, 0% to 20% of low substituted hydroxypropyl cellulose, a lubricant, and an effective amount of a pharmaceutically active agent, wherein said tablet exhibits disintegration within 1 to 15 seconds when tested in an *in vitro* disintegration test.

28. The pharmaceutical tablet according to claim 27, wherein said tablet further comprises flavorants, colorants, or both.

29. Use of silicified microcrystalline cellulose for making an orally disintegratable pharmaceutical tablet.

30. A process of rapidly releasing an active agent from a solid tablet, which comprises disintegrating a tablet according to claims 1-26, by placing the tablet in a water environment.

31. The process according to claim 30, wherein said water environment is an oral cavity.

32. The process according to claim 30, wherein said water environment is a water-filled container.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/004119

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/110578 A1 (KHANKARI RAJENDRA K ET AL) 15 August 2002 (2002-08-15) page 3, column 2, paragraph 37 claim 1	1-32
X	US 6 471 994 B1 (STANIFORTH JOHN N ET AL) 29 October 2002 (2002-10-29) column 6, line 9 - line 13 column 6, line 32 - line 33 examples 10-12 claims 1-5	1-32
P,X	WO 2004/000281 A (LEK PHARMACEUTICALS D D ; SKULJ VESNA (SI); JENKO OSEL MAJA (SI); SIRC) 31 December 2003 (2003-12-31) examples 1-6 claims 1,17	1-32

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
15 July 2004	26/07/2004

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/000197 A (HERMAN MARK ; FRISBEE STEVEN (US); MEZAACHE NAIMA (US); WOODALL PATRIC) 31 December 2003 (2003-12-31) page 35 claim 1	1-32
P,X	WO 03/063831 A (CREW MARSHALL DAVID ; FRIESEN DWAYNE THOMAS (US); SCHADTLE STEPHEN JOS) 7 August 2003 (2003-08-07) page 43; example 8 claim 1	1-32

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/004119

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002110578 A1	15-08-2002	US 6200604 B1	13-03-2001
		US 2003091629 A1	15-05-2003
		AU 4019400 A	16-10-2000
		CA 2333375 A1	05-10-2000
		EP 1082106 A1	14-03-2001
		EP 1419765 A1	19-05-2004
		EP 1417959 A1	12-05-2004
		JP 2002540141 T	26-11-2002
		WO 0057858 A1	05-10-2000
		US 6576250 B1	10-06-2003
US 6471994 B1	29-10-2002	US 6103219 A	15-08-2000
		US 5725884 A	10-03-1998
		US 5585115 A	17-12-1996
		US 2003147949 A1	07-08-2003
		US 2003096005 A1	22-05-2003
		US 6217909 B1	17-04-2001
		US 2001001664 A1	24-05-2001
		US 2002142032 A1	03-10-2002
		US 6106865 A	22-08-2000
		AT 239450 T	15-05-2003
		AU 698667 B2	05-11-1998
		AU 4759896 A	31-07-1996
		AU 708346 B2	05-08-1999
		AU 5019996 A	07-08-1996
		AU 5830399 A	06-01-2000
		BR 9605245 A	16-09-1997
		BR 9605329 A	16-09-1997
		CA 2183881 A1	18-07-1996
		CA 2183882 A1	25-07-1996
		DE 69627934 D1	12-06-2003
		DE 69627934 T2	12-02-2004
		DK 752848 T3	01-09-2003
		EP 1287823 A1	05-03-2003
		EP 0752848 A1	15-01-1997
		EP 0749300 A1	27-12-1996
		ES 2199281 T3	16-02-2004
		FI 963496 A	06-11-1996
		FI 963497 A	06-11-1996
		HU 9602360 A2	28-08-1997
		HU 9602361 A2	28-08-1997
		IL 116674 A	29-05-2003
		IL 116675 A	31-10-2000
		IL 139728 A	24-06-2003
		JP 3300364 B2	08-07-2002
		JP 10500426 T	13-01-1998
		JP 10512862 T	08-12-1998
		NO 963732 A	08-11-1996
		NO 963733 A	06-09-1996
		PT 752848 T	29-08-2003
		TW 505529 B	11-10-2002
		WO 9622080 A1	25-07-1996
		WO 9621429 A1	18-07-1996
		US 2003099702 A1	29-05-2003
		US 5725883 A	10-03-1998
		US 5866166 A	02-02-1999
		US 5741524 A	21-04-1998
		US 5948438 A	07-09-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/004119

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6471994 B1		US 5858412 A	12-01-1999
WO 2004000281 A	31-12-2003	SI 21221 A	31-12-2003
		WO 2004000281 A1	31-12-2003
WO 2004000197 A	31-12-2003	US 2003124184 A1	03-07-2003
		WO 2004000197 A2	31-12-2003
WO 03063831 A	07-08-2003	WO 03063831 A2	07-08-2003
		US 2003224043 A1	04-12-2003